Controlling immunity balances the brain in health and disease

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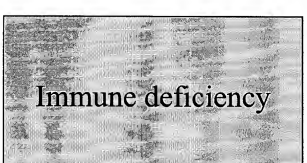
Homeostasis

Levels of immune activity

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.



Why neurodegenerative conditions are associated with a wide-spread loss of neurons:

- Poor spontaneous neurogenesis (limited formation of new neurons)
- Poor spontaneous regeneration (poor re-growth)
- Diffuse damage due to high vulnerability to defense mechanism unless tightly controlled -'domino effect'

Common view of inflammation in neurodegenerative conditions

- In most neurodegenerative diseases there is a local inflammatory response.

- This local inflammatory response (mediated by adaptive and/or innate immunity) has collectively received a bad reputation.

Our concept: The immune system plays a key role in Central Nervous System

maintenance

Renewal

Plasticity

We argue against bad or good innate/adaptive immunity or against good/bad cytokines in the context of the CNS; immune response should be tightly controlled rather than suppressed - suppression over time denies the key players in brain's maintenance and repair

Degenerative conditions and consequences of defense battle

Enemies within

Accumulating self compounds (e.g. gangliosides, β-amyloid, Prion, S-Ag, etc.)

Ionic imbalance

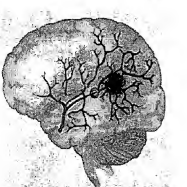
Free radicals

NO

glutamate

Metabolic deficit

Growth Factors (Neurotrophins



Consequences of defense

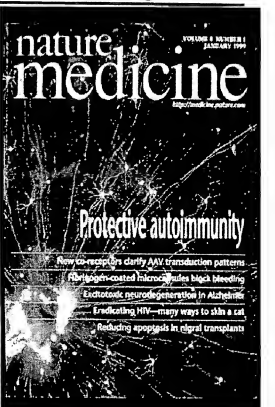
Malfunctioning microglia

Inflammation-associated Toxicity (NO, TNF-a, COX-2)

Neuronal death

Immune cells are needed for CNS maintenance and repair "Protective autoimmunity"

- Protective autoimmunity: **A controlled T-cell response recognizing CNS antigens protects against internal enemies**
- **Autoimmune disease: An outcome of malfunctioning of autoimmunity**
- Tolerance to self: **Ability to tolerate response to self without developing an autoimmune disease**
- Specificity provides the T cells with a way of homing and local reinforcement/activation.



Rapalino et al., Nat. Med., 1998; Moalem et al., Nat. Med.1999; Schwartz et al., TINS, 1999, 2003;Hauben et al. J. Neurosci., 2000, 2003; Schwartz and Kipnis, Trends Immunol., 2002; Yoles et al., J. Neurosci. 2001; Kipnis et al., PNAS, 2001, 2003;Kipnis et al., J. Neurosci., 2003; Mizrahi et al.,J. Immunol., 2002.

Posttraumatic therapeutic vaccination with modified myelin self-antigen prevents complete paralysis while avoiding autoimmune disease

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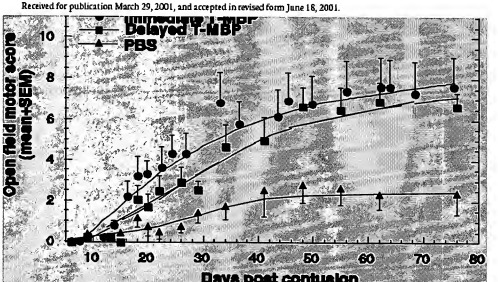
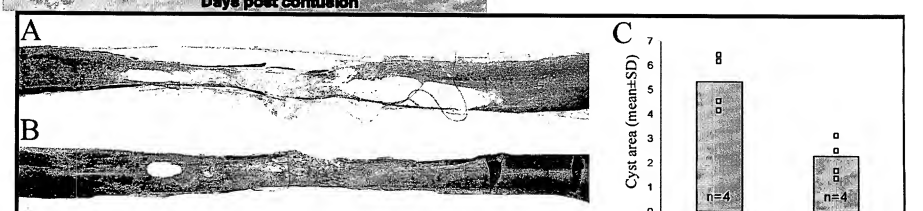
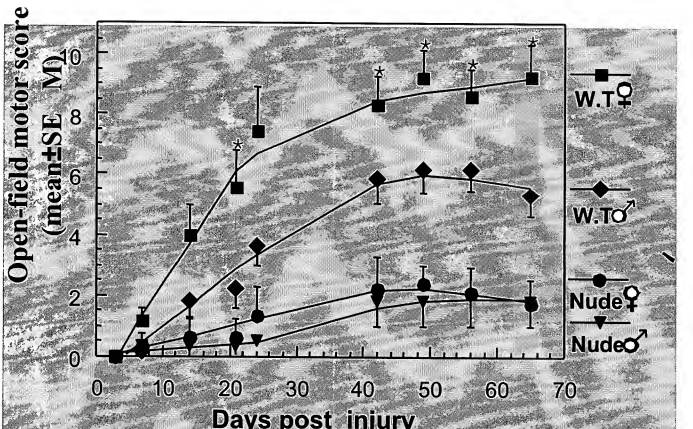




Immune compromise animals have a weak ability to cope with spinal cord injury



Hauben et al., Eur. J. Neurosci., 2002

T cells

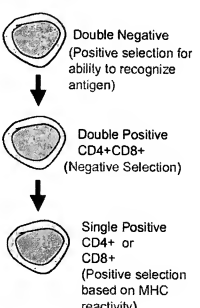
Recognizing Self

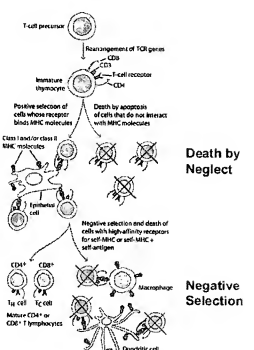
(nature mistake or purposeful selection?)

Recognizing non-self (intruders)

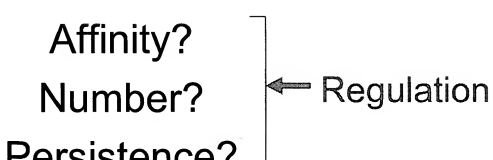
(fighting against intruders)

T-Cell Selection - Overview

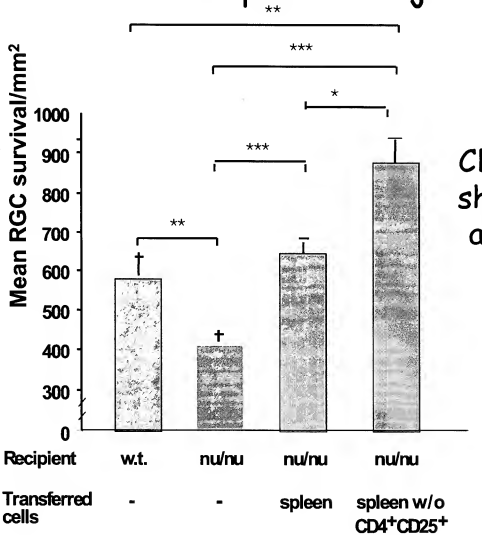




What is the difference between beneficial and disease-causing autoimmune T cells?



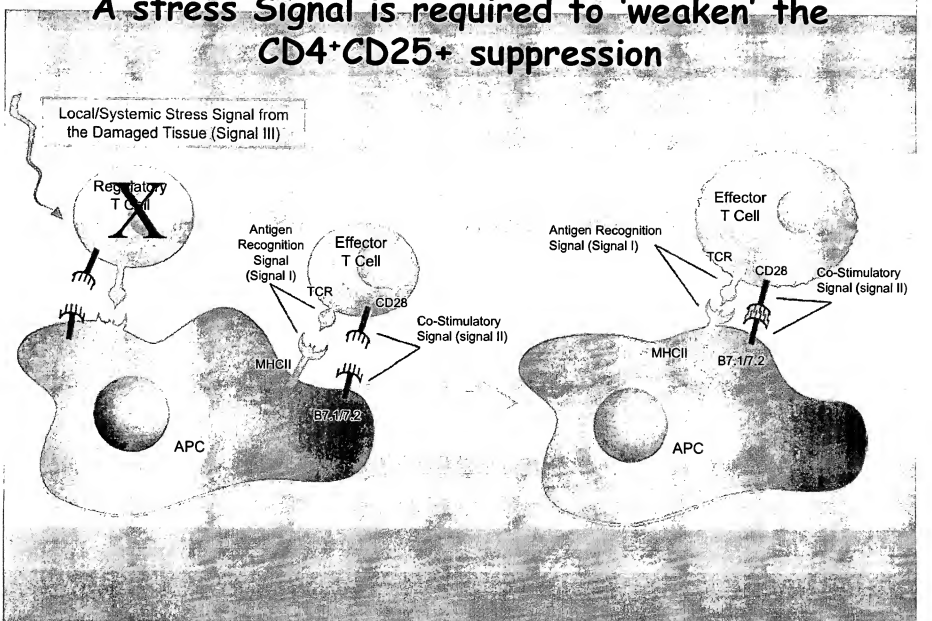
Depletion of regulatory T cells increases ability to cope with injurious conditions



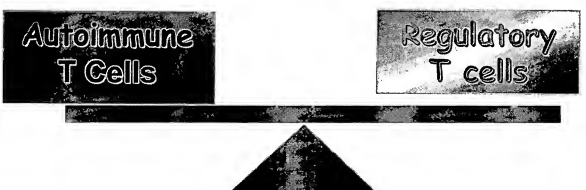
Nu/nu mice recipient of splenocytes depleted of $CD4^+CD25^+$ regulatory T cells show better neuronal survival after CNS injury, compared to recipient of whole splenocytes

Kipnis et al., PNAS, 2002

What is needed to evoke autoimmunity?
A stress Signal is required to 'weaken' the $CD4^+CD25^+$ suppression



Balance Between Autoimmune T cells and Regulatory T cells



Autoimmune-dependent CNS Homeostasis

Malfunction

Too much

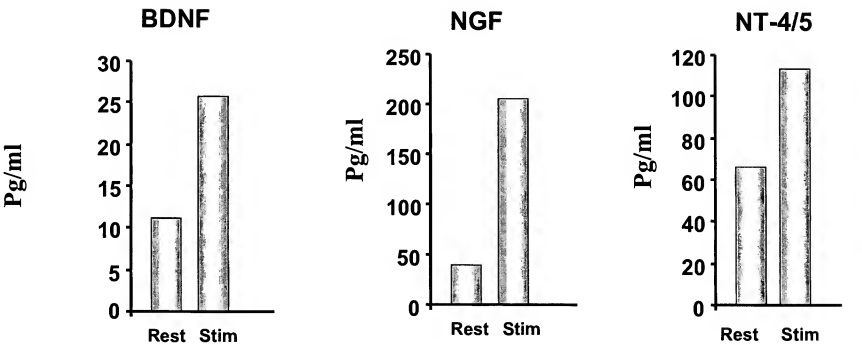
Autoimmune disease

Too much

Neuronal loss
Limited neurogenesis

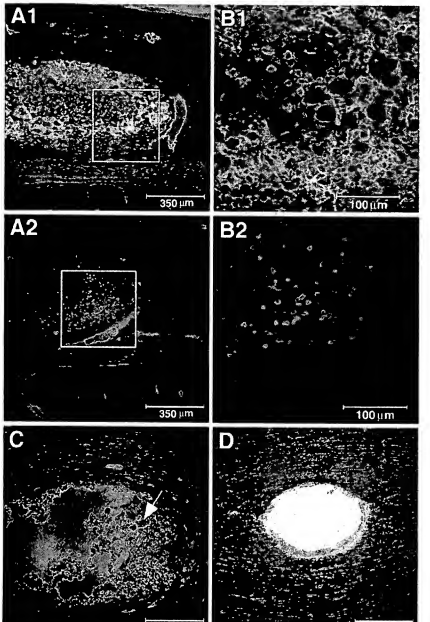
The underlying mechanism

T cells provide a mobile mini-factory; secrete higher levels of neurotrophic factors upon activation

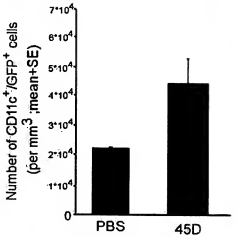


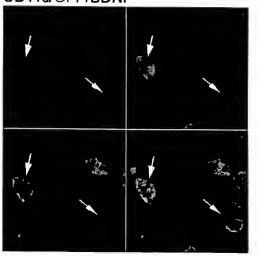
Moalem et al., J. Autoimmun, 2000;
Kipnis et al., PNAS, 2000

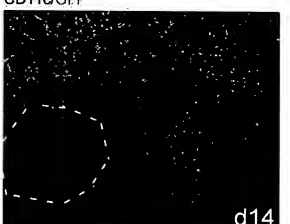
T cells control microglia/macrophage behavior

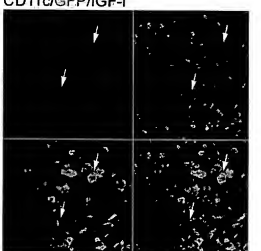


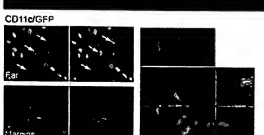
Butovsky et al.,
FASEB J., 2001



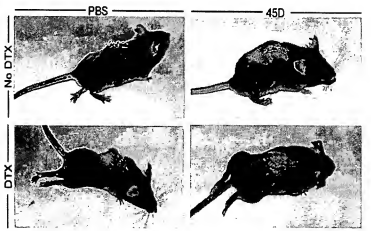




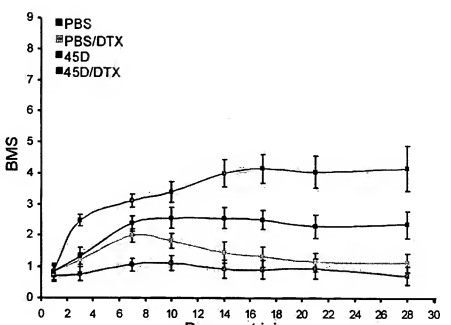


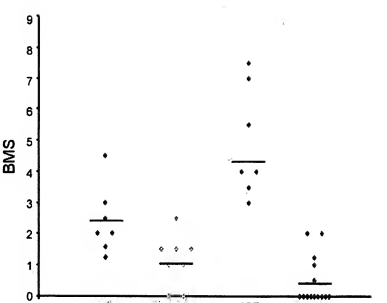


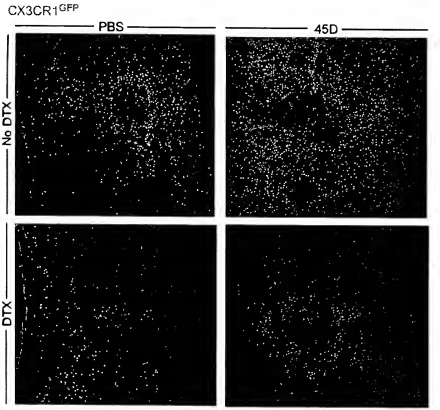
T cells enhance recruitment of blood-borne monocytes, expressing IGF-I and dendritic-like phenotype



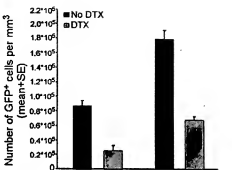
Selective depletion of blood-borne monocytes expressing CD11c completely impaired recovery

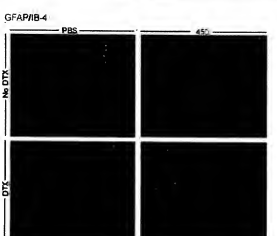


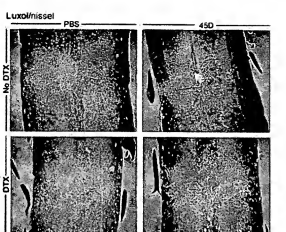




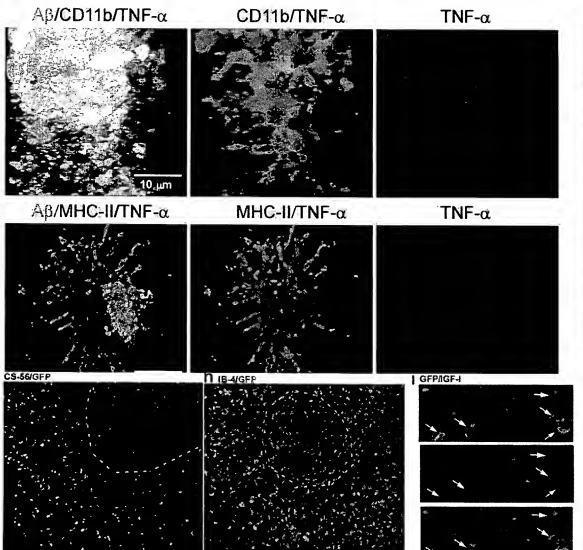
Depletion of CD11c+/GFP+ bone marrow-derived monocytes worsened recovery

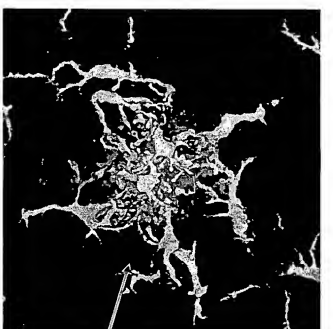






CNS specific T cells are needed for creating an immunological niche: microglial phenotype switch and recruitment of blood-borne monocytes





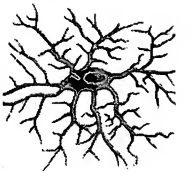
Butovsky et al., PNAS 06

Butovsky et al., EJNS 07

GFP Monocytes in chimeric mice

Rolls and Shechter 07

Microglia function as stand-by resident immune cells



Bad

Innate activation
Neurodegeneration

Immune functions -

killing and removal of microorganisms

Secretion of:
NO, TNF-a, COX-2

good

overwhelmed

Activation by adaptive immunity

Protection

Immune and neural functions:

- Delivery of neurotrophic factors and cytokines
- Removal of growth inhibition (e.g. myelin phagocytosis)
- Buffering of toxicity mediators (e.g. Glutamate clearance)
- Antigen presenting cells

Destruction

Overwhelming activation:

TNF-a counteract the benefit

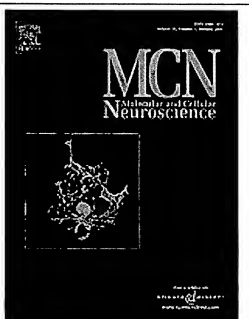
The underlying mechanism

•T cells serve as a mobile mini- factory producing locally cytokines and growth factors (Moalem et., Nat. Med. 1999; J. Autoimmunity 2000; Kipnis et al., PNAS 2000)

•T cells depending on their phenotypes 'shape' microglial activity and confer them with ability to (a) produce IGF-I and BDNF, (b) act as antigen presenting cells (c) support neural tissue survival, (d) buffer glutamate, and (d) to support cell renewal

•(Butovsky et al., FASEB J., 2001; Mol. Cell. Neurosci., 2005, 2006; Shaked et al., J.Neurochem., 2005; J.Clin. Inves., 2006; Ziv et al., Nat. Neurosci., 2006).

Working Hypothesis: Our in vitro findings that T cell-activated microglia can support cell renewal from adult neural stem cells suggest that the primary role of microglia is to maintain neuronal survival and neurogenesis/oligodendrogenesis in a healthy adult brain, their role in diseased conditions is an extension of this primary role



Butovsky, Ziv et al. Mol. Cell. Neurosci., 2005, 2006

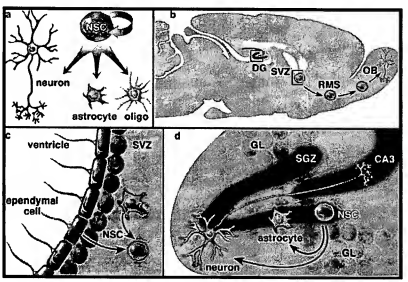
Cell renewal in the adult CNS

Nat Med. 1998 Nov;4(11):1313-7.

Neurogenesis in the adult human hippocampus.

Eriksson PS, Perfilieva E, Björk-Eriksson T, Alborn AM, Nordborg C, Peterson DA, Gage FH

Neurogenesis at adulthood is restricted to hippocampus and olfactory



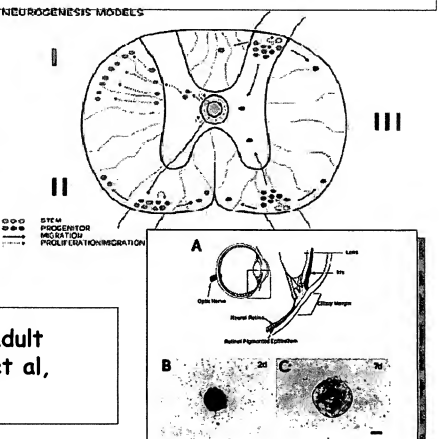
J Neurosci. 2000 Mar 15;20(6):2218-28.

FREE ACCESS ONLINE
www.jneurosci.org

Proliferation and differentiation of progenitor cells throughout the intact adult rat spinal cord.

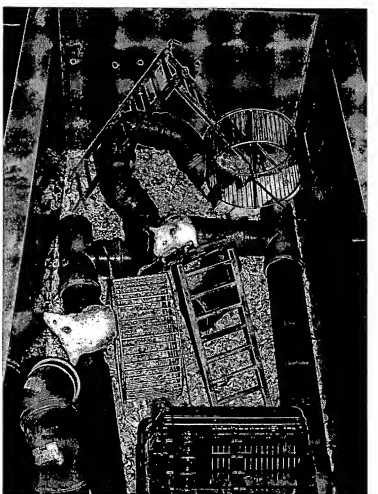
Horner PJ, Power AE, Kempermann G, Kuhn HG, Palmer TD, Winkler J, Thal LJ, Gage FH

Stem cell proliferation and migration in the intact adult spinal cord

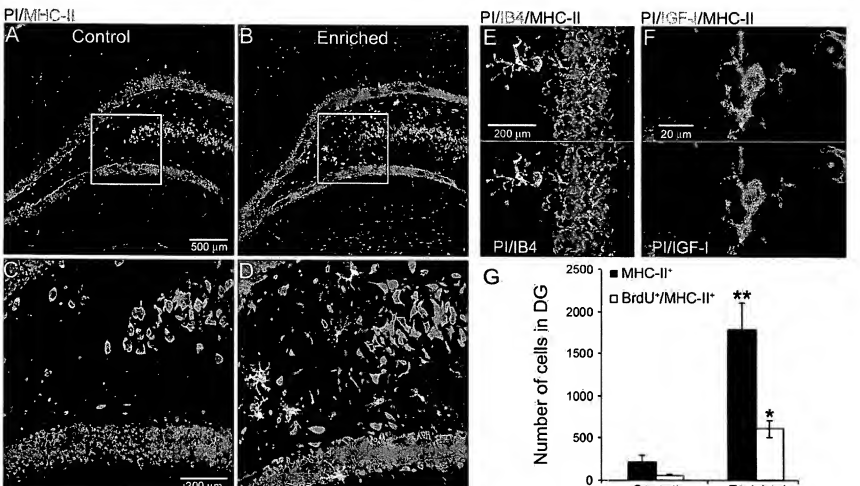


Retinal stem cells in the adult mammalian eye (Tropepe et al, Science 2000)

Enriched Environment boosts formation of new neurons in the brain from a pool of adult stem cells



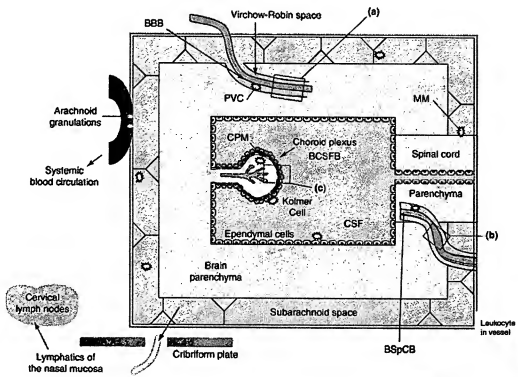
Neurogenesis induced by enriched environment is associated with microglia expressing a T-cell-activated phenotype



Ziv, Ron, Butovsky, et al., Nat. Neurosci., 2006

Are T cells contributing to the maintenance of the adult neurogenic niche?

Routes for circulating leukocytes to cross blood-CNS barriers



-The CSF of healthy individuals contains 150,000 T lymphocytes

-Half of which are activated

–A small population of mature dendritic cells can be detected in human CSF

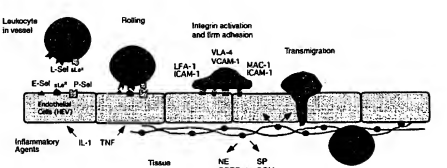
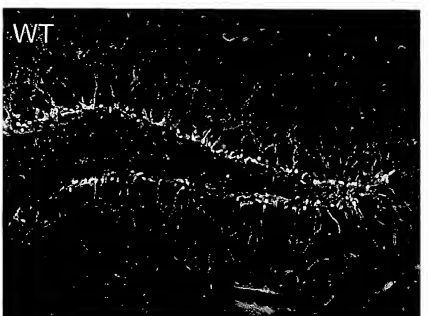
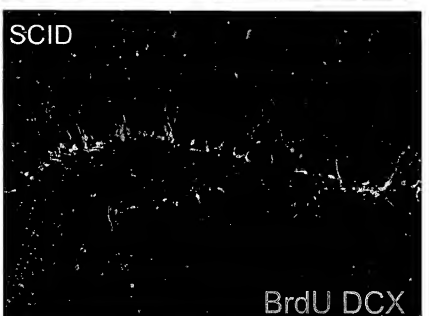
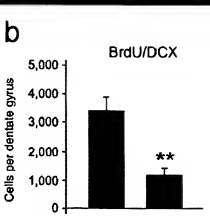


FIGURE 1 Leukocyte adhesion to endothelial cells and migration into tissues. Leukocyte adhesion and migration is a multistep process that initially involves (a) leukocyte rolling, (b) stimulation of integrins and firm adhesion, and (c) diapedesis into the tissues. Catecholamines such as norepinephrine (NE) and neuropeptides [calcitonin gene-related peptide [CGRP], substance P [SP], somatostatin [SOM], neuropeptide Y [NPY], vasoactive intestinal peptide [VIP] present in nerve terminals surrounding blood vessels or contained in the tissue parenchyma can modulate this process.

Adult Neurogenesis is impaired in immune deficient mice

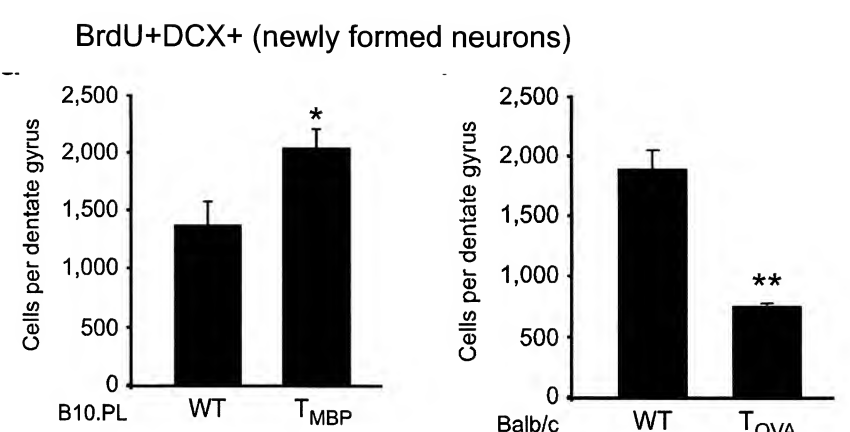






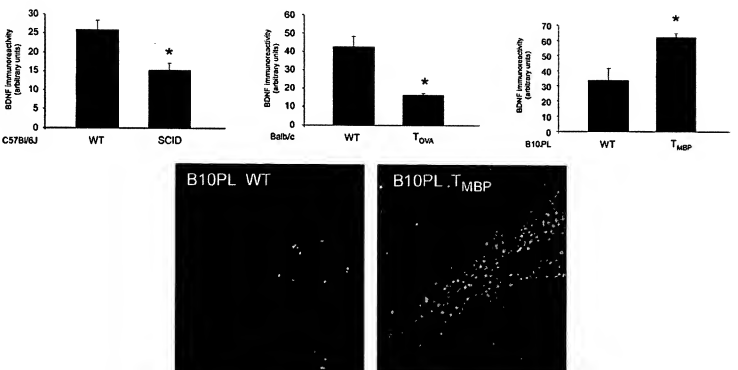
Ziv, Ron, Butovsky et al., Nature Neurosci. 2006

The T cells needed for adult neurogenesis are CNS specific



Ziv, Ron, Butovsky et al., Nature Neurosci. 2006

BDNF expression is T-cell related: Association with hippocampal neurogenesis and learning abilities



Ziv, Ron, Butovsky et al., Nature Neurosci. 2006

Leading Edge

Neurobiology Select

The formation of new neurons (neurogenesis) results from the complex interplay of many variables: cell proliferation, migration, cell fate choice, and survival. Recent papers identify factors involved in each of these aspects of neurogenesis and indicate how these variables may be integrated during development and adulthood. This recent work includes the report of a kinase that controls cell division in neural progenitors and a study suggesting that autoimmune T cells are positive regulators of neurogenesis. Other intriguing findings link planar cell polarity to neural tube development in zebrafish and the migration of neuroblasts in adult mice.

Autoimmunity Gives Neurogenesis a Lift

Given the link between autoimmunity and diseases such as multiple sclerosis, it is no wonder that T cells in the brain that recognize self-antigens have a bad reputation. However, new work by Schwartz, Kipnis, and colleagues argues (Ziv et al., 2006) for a more complex view of these much maligned cells. Their work suggests that, rather than always being detrimental, self-recognizing T cells can also support neurogenesis in adult mice if well-controlled. Previous work from the Schwartz lab has shown that the recruitment of autoimmune T cells to sites of neuronal injury promotes neural cell survival by altering the behavior of local microglia. This new report suggests that similar immune-based mechanisms may also operate during normal adult neurogenesis. In support of their argument, Ziv et al. (2006) demonstrate that neurogenesis is impaired in the hippocampus of immune-deficient mice. Moreover, unlike wild-type mice, neurogenesis in immune-deficient mice is not stimulated by enriching the mouse's environment. Remarkably, neurogenesis is restored by the introduction of autoimmune T cells that recognize a self-antigen (in this case myelin basic protein) but is not restored by T cells that recognize a non-self-antigen. The presence of autoimmune T cells also improves the performance of mice in the Morris water maze, a spatial memory task that has been linked to neuronal activity in the hippocampus. One of the far-reaching implications of the study is that it suggests mechanisms by which age-related changes in the immune system could be linked to cognitive decline in humans. Future work may also establish the precise mechanisms by which T cells regulate microglia to foster an environment that supports neuronal survival.

Y. Ziv et al. (2006). Nature Neuroscience. Published online January 15, 2006. 10.1038/nn1629.

How can protective autoimmunity be boosted and developed as a therapeutic approach?

- Weak self-antigen (cryptic)
(Fisher et al., J. Neurosci., 2001;
- Altered self-antigen (APL)
(Hauben et al., J. Clin. Invest., 2001);
- Dendritic cells
(Hauben, Gothilf et al., 2003)
- Random copolymers
(Kipnis et al., PNAS 2000; Schori et al., PNAS 2001)
- Pharmacological blocking of Treg
(Kipnis et al,.2004)
- Homeostasis-driven
Proliferation of lymphocytes
(lymphopenia; Kipnis et al., EJN, 2004)

Boost

Self-reactive T-cells

Down regulate

CD4+CD25+
Regulatory T-cells

Down
regulate

Poly (YE)

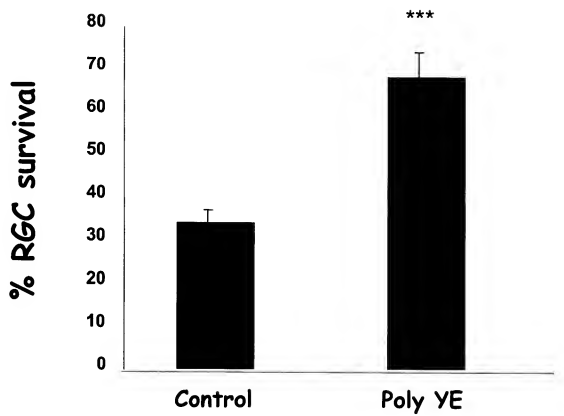
CD4+CD25+
Regulatory T-cells

1. Random polymer
2. Evokes strong immune response in mice
3. Down regulates a subpopulation of regulatory T cells resulting in a speedy recruitment of the relevant autoimmune T cells

Proof of concept

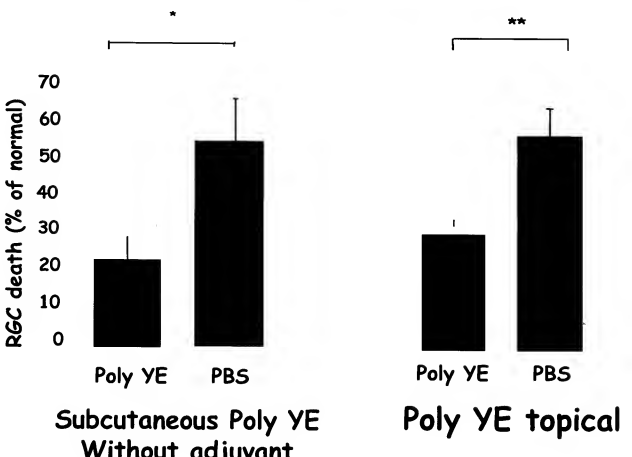
Glutamate toxicity

Proof of concept
Glutamate toxicity

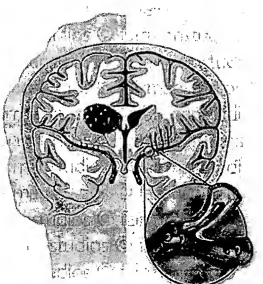


Poly YE Neuroprotective effect in animal models of CNS disorders

Acute glaucoma



Stroke

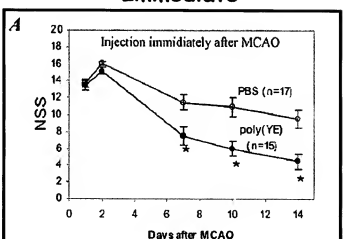


Middle cerebral artery occlusion (MCAO)

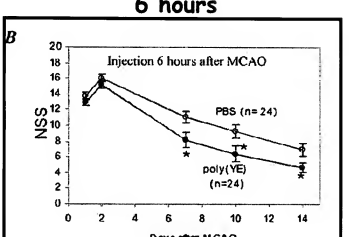
Poly(YE) - up to 24 h therapeutic time window

in permanent MCA-occlusion (stroke)

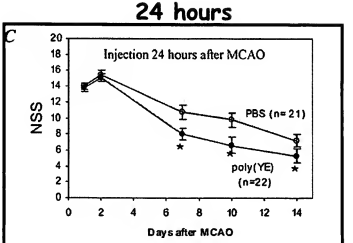
Immediate



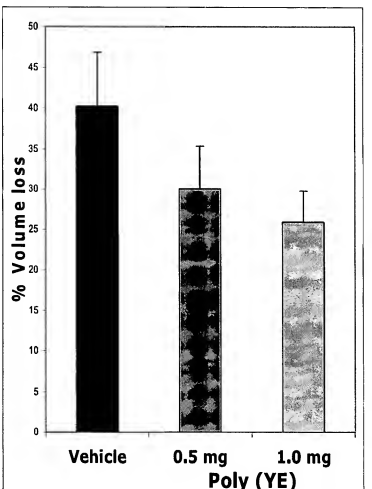
6 hours



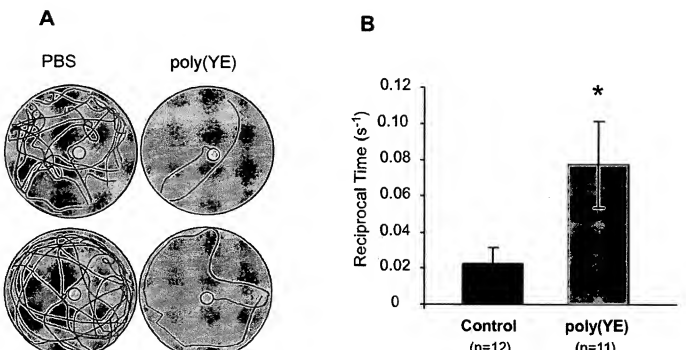
24 hours



Poly(YE) decreases volume loss starting from the subacute phase



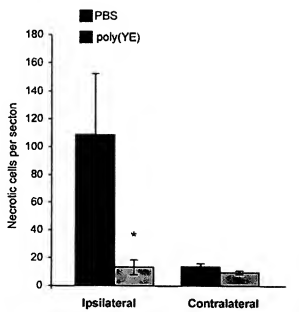
Poly (YE) protects from behavioral deficits following stroke

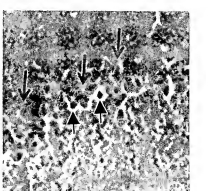


Poly (YE)- treated group learned and remembered the place of the platform unlike the control group

Poly (YE) attenuates hippocampal neuronal death following stroke

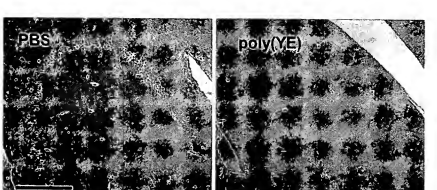
A



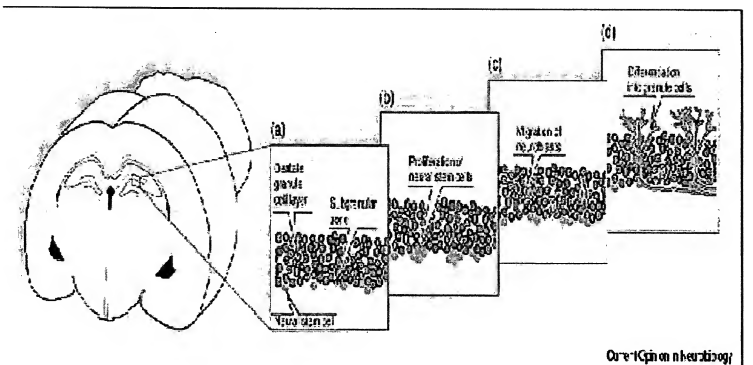


Normal cells
Necrotic cells

B



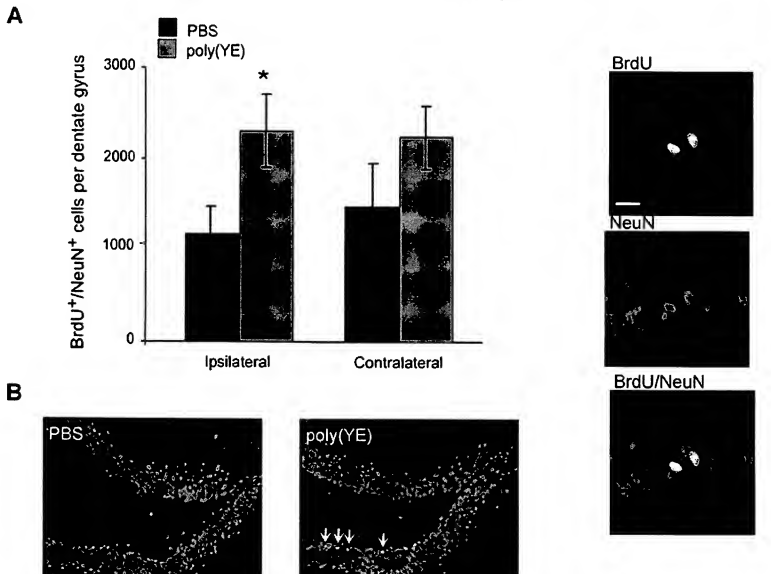
Neurogenesis following stroke



Hippocampal neurogenesis is increased after cerebral ischemia

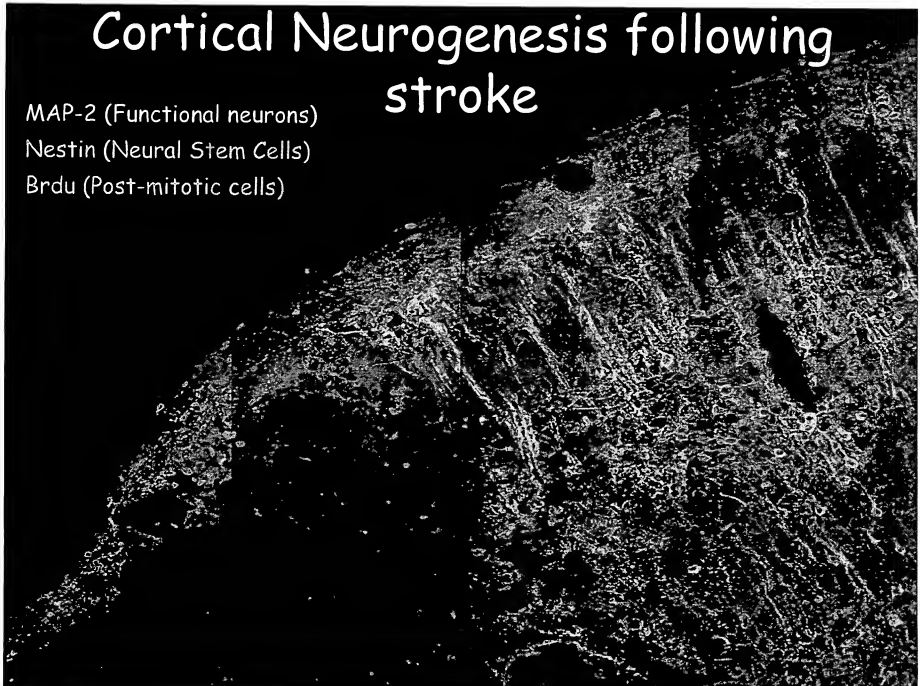
Nakatomi et al, Cell 2002
Kokaia & Lindvall, Cur Opin Neurobiol, 2003

Therapeutic vaccination with poly(YE) enhances hippocampal neurogenesis following stroke

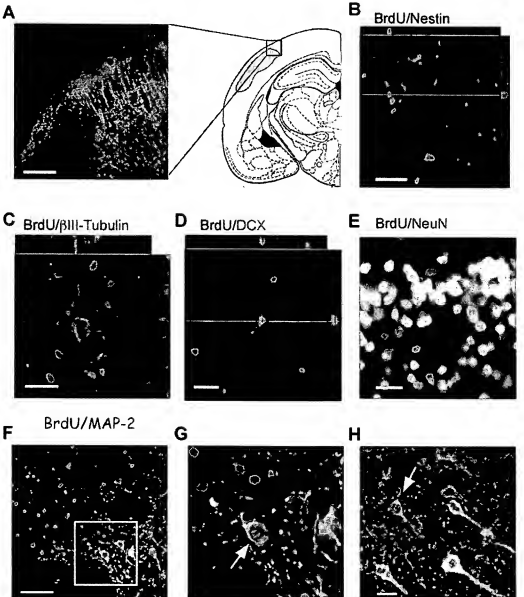


Cortical Neurogenesis following stroke

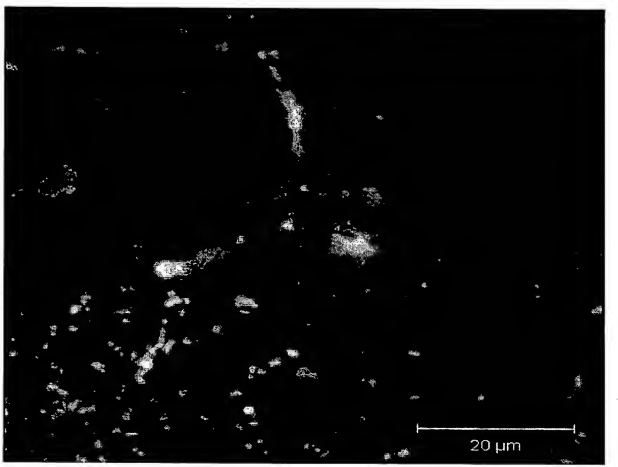
MAP-2 (Functional neurons)
Nestin (Neural Stem Cells)
Brdu (Post-mitotic cells)



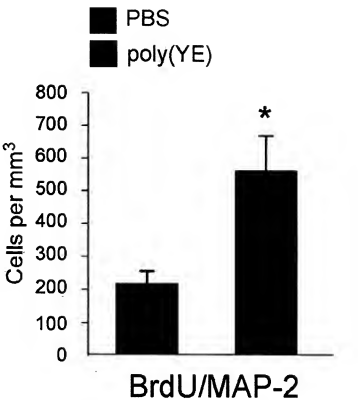
Formation of new neurons in the Cortex



Formation of new neurons in the Cortex

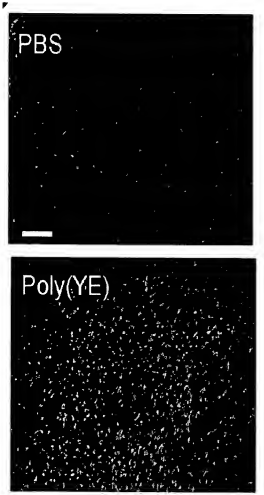


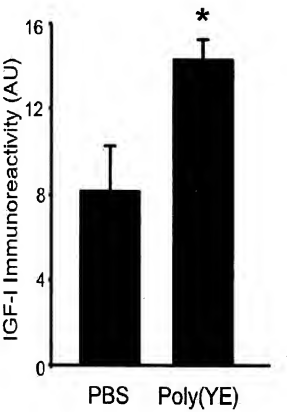
Poly(YE) augments cortical neurogenesis



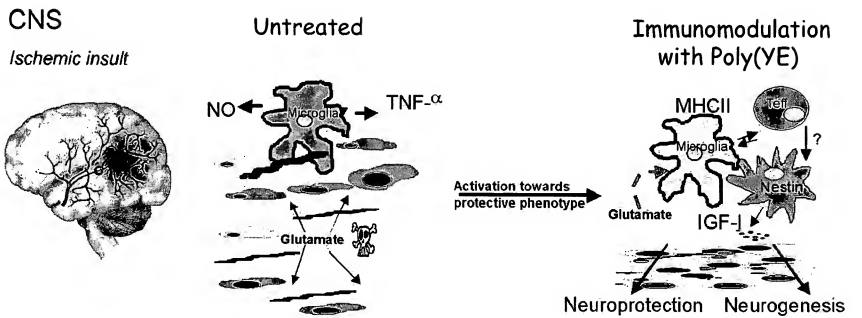
Neurogenesis in a non-neurogenic area

IGF-1 production is increased following Poly(YE)





Putative model of the neuroimmune interactions in the ischemic brain after poly(YE) treatment

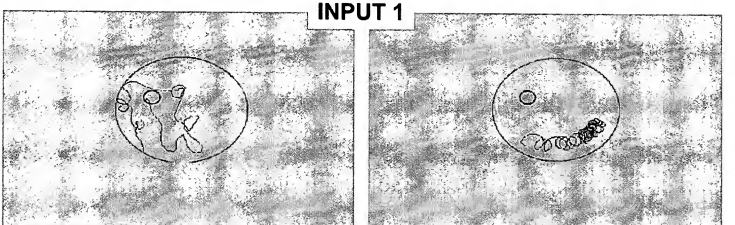


Mental disorders

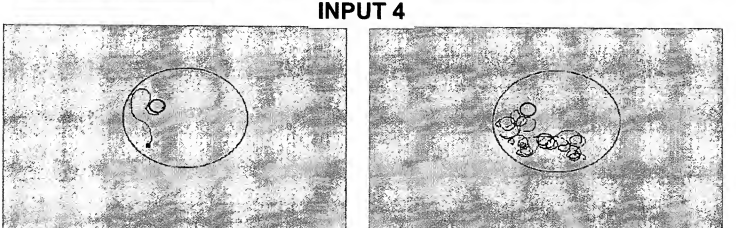
MK-801 + Poly YE

MK-801 + Poly YE

INPUT 1



INPUT 4



Protective immunity

Mechanism of action

Poly YE an immune modulator - augments the injury induced protective immunity by its effect on the local immune response

Poly YE restore tissue homeostasis – shapes microglial activity to eliminate toxic elements from the injured environment and to secrete trophic and growth factors, supportive of neuronal survival

Poly YE enhances tissue repair – creates environmental conditions supportive of neurogenesis